Harvey Lodish et al., Molecular Cell Biology (3rd ed, 1995, Scientific American Books, NY)

kinase cascade, they often generate different cellular responses. Several factors could account for the varying responses observed in different cell types: activation of additional pathways in some cells; differences in the transcription factors or other proteins phosphorylated by activated MAP kinase; or differences in the substrates of these phosphorylated proteins. Recent genetic studies in yeast have shown that there are at least three different MAP kinase pathways mediating different signals. This suggests that multiple MAP kinase signaling pathways probably also will be uncovered in animal cells.

➤ *Other Important Second Messengers*

As we discussed earlier in this chapter, cAMP is widely used as the second messenger in signaling systems in animals. The synthesis and degradation of cAMP are regulated by many seven spanning G_s or G_i protein–linked receptors but not, so far as is known, by any RTKs. Three other molecules—Ca^{2+}, inositol 1,4,5-trisphosphate, and 1,2-diacylglycerol (see Figure 20-3)—function as second messengers in signaling pathways initiated by both seven-spanning receptors and RTKs.

We first discuss how a rise in cytosolic Ca^{2+} ions induces various metabolic responses and then consider how many hormones acting through inositol 1,4,5-trisphosphate (IP_3) cause this rise in the cytosolic Ca^{2+} level. We also examine the role of 1,2-diacylglycerol (DAG) in regulating other cellular functions. Both IP_3 and DAG are formed from the same precursor, and signaling pathways involving these second messengers sometimes are referred to as *inositol-lipid pathways*. All of these second messengers interact in complex circuits to regulate crucial aspects of the growth and metabolism of cells.

Cellular Effects of Ca^{2+} Depend on Its Cytosolic Level and Often Are Mediated by Calmodulin

Most intracellular Ca^{2+} ions are sequestered in the mitochondria and endoplasmic reticulum (ER) or other cytoplasmic vesicles. The concentration of Ca^{2+} ions free in the cytosol usually is kept below 0.2 μM. Ca^{2+} ATPases pump cytosolic Ca^{2+} ions across the plasma membrane to the cell exterior or into the lumens of the endoplasmic reticulum or other intracellular vesicles that store Ca^{2+} ions (see Figure 15-11). Localized increases in the cytosolic level of free Ca^{2+} is critical to its function as a second messenger. Local concentrations of Ca^{2+} ions can be monitored with fluorescence dyes; in large cells, different Ca^{2+} concentrations can actually be detected in specific regions of the cytosol (see Figures 5-12 and 5-13).

Small increases in the level of cytosolic Ca^{2+}, which often are mediated by a rise in IP_3, trigger many cellular responses (Table 20-7). In secretory cells, such as the insulin-producing β cells in the pancreatic islets, a rise in

TABLE 20-7 Cellular Responses to Hormone-Induced Rise in Inositol 1,4,5-Trisphosphate (IP_3) and Subsequent Rise in Cytosolic Ca^{2+} in Various Tissues

Tissue	Hormone Inducing a Rise in IP_3	Cellular Response
Pancreas (acinar cells)	Acetylcholine	Secretion of digestive enzymes, such as amylase and trypsinogen
Parotid (salivary gland)	Acetylcholine	Secretion of amylase
Pancreas (β cells of islets)	Acetylcholine	Secretion of insulin
Vascular or stomach smooth muscle	Acetylcholine	Contraction
Liver	Vasopressin	Conversion of glycogen to glucose
Blood platelets	Thrombin	Aggregation, shape change, secretion of hormones
Mast cells	Antigen	Histamine secretion
Fibroblasts	Peptide growth factors, such as bombesin and PDGF	DNA synthesis, cell division
Sea urchin eggs	Spermatozoa	Rise of fertilization membrane

SOURCE: M. J. Berridge, 1987, *Ann. Rev. Biochem.* 56:159–193; M. J. Berridge and R. F. Irvine, 1984, *Nature* 312:315–321.